REMARKS

DETAILED ACTION

1. Applicant thanks Examiner Lucas and Supervisory Patent Examiner Housel for the interview of April 22, 2005. A summary of the interview is provided separately.

Currently, claims 1-12 are pending in the application, with claims 1-9 under consideration to the extent that they read on, or are generic to the elected invention. Claims 10-12 are withdrawn as to non-elected inventions. Claims 1-9 were rejected in the prior action, mailed on December 17, 2003. Claim 2 has been cancelled without prejudice. The Applicant submitted a Response on March 16, 2004.

No new matter has been added.

Specification

2. **(Prior Objection- Withdrawn)** The disclosure was objected to because of the following informalities: on page 54, line 16 of the specification, the application indicates that Table 1 discloses the results of the use of anti-HIV test of the claimed composition. However, Table 1, on page 43, discloses the amino acid profile of a typical blood composition. It appears as though the application should refer to Table 3 in this instance. In view of the amendment of the application, the objection is withdrawn.

Applicant thanks the Examiner for withdrawing the objection.

Claim Rejections – 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. **(Prior Rejection- Maintained)** The Examiner rejected claims 3 and 4 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner asserted that these claims read on immunogenic compositions comprising a "reduced viral pathogen." The Examiner further stated that it was not clear from the claims or the specification what is meant by the term "reduced."

The term "reduced" has been deleted from claim 3. In consequence, withdrawal of the rejection of claims 3 and 4, as amended, under 35 USC §112 ¶2 is respectfully requested.

In addition, claim 4 (and claim 7) have been clarified, by, for example, removing redundant terms.

5. **(Prior Rejection- Withdrawn)** Claim 7 was rejected under 35 U.S.C. 112, second paragraph, as being indefinite because it was not clear what was meant by the phrase "fungi influenza virus." In view of the amendment of the claim to insert a comma between the terms fungi and influenza virus, the rejection is withdrawn.

Applicant thanks Examiner for withdrawing the rejection.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. **(Prior Rejection- Restated and Maintained)** The Examiner rejected claims 3-9 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for immunogenic compositions comprising an inactivated influenza virus, does allegedly not reasonably provide enablement for vaccine compositions, or compositions inducing immunity against, any viral pathogen. According to the Examiner, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. Further, it is known in the art that whole viruses can

induce an immune response. Thus, the Examiner concludes, there is nothing to exclude whole live virus in the claimed compositions.

According to the MPEP "For a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art...would expect the claimed genus could be used in that manner without undue experimentation." MPEP 2164.02.

The Examiner has agreed that the immunogenic compositions comprising an inactivated influenza virus are enabled by the specification.

The specification provides many additional examples, including:

1) a shrimp composition comprising baculovirus. See Example 12 for preparation of the immunogen and Example 13 for use as a preventative vaccine.

2) a sputum composition comprising mycobacterium tuberculosis or *Tuberculum bacilli*. See Example 22.

The specification also has the second element identified by the MPEP, that is, the requisite statement applicable to the genus as a whole, e.g.: "Generally, according to this invention any infected tissue as a starting material is adequate and suitable." Page 35, lines 15-16.

Moreover, the specification discloses extensive details of the preparation of immunogen from infected blood (e.g., page 35, line 16-page 36, line 3), of thermal denaturation of antigen (e.g., page 28, lines 27-32, and page 29, lines 19-23), of use of acid or base co-treatment of antigen (e.g. page 29, line 24-page 30, line 6), and other procedures. With the information provided one of skill in the art can prepare immunogenic preparations from a wide variety of sources of antigens without undue experimentation.

Thus, Applicant has enabled the preparation of not merely influenza immunogen but also provided specific details of the preparation of several additional viral pathogens. Applicant has

also taught general methods suitable for preparation of many immunogens and compositions suitable for eliciting an immune response.

In addition the following information is provided with, and incorporated into, this Reply: HIV Clin. Trials 2002;3(3):258-259; HIV Clin. Trials 2002;3(1):21-26; Electronic Journal of Biotechnology ISSN: 0717-3458, vol. 6, no. 1, April 15, 2003; Vaccine 21 (2003) 624-628; Current Pharmaceutical Design, 2003, 9 (18): 1419-1431; Acta virologica **48**: 73-78, 2004; European Journal of Clinical Nutrition (2004) 58, 110-115; Journal of Clinical Virology 744 (2004), 1-8; Viral Immunology 16(4), 2003, 427-445. The information in these references shows that mucosal vaccines formulated as pills have been prepared against a wide variety of agents using the method of the invention.

In particular, use of a multivalent vaccine prepared from blood of patients having clinical HIV infections showed anti-hepatitis activity in that enzyme markers of hepatic dysfunction improved substantially in a 61-member patient population. Electronic J. Biotechnology 6(1) April 15, 2003. The effect was statistically significant at the $p=0.02$ level. *Id.* Moreover, use of the same multivalent vaccine in another nutritionally wasted patient population resulted in a significant weight gain that was statistically significant at the $p<0.001$ level. European J. Clinical Nutrition (2004) 58, 110-115. Yet again, the same multivalent vaccine increased survival in a group of terminally-ill (end stage) AIDS patients. HIV Clin. Trials 2002; 3(3): 258-259. The control group that did not receive the vaccine had a maximum survival of 2 months. *Id.* The group that received at least one oral vaccine pill survived up to 2 years. *Id.* Some patients in the latter group continued on a once-daily pill regimen. *Id.* In addition, vaccine directed to influenza H5N1 has been shown promise in reducing "bird flu" infections in chicken flocks, when provided at a sufficiently high dose, see Dr. Bourinbaiar's affidavit.

Thus, a therapeutic efficacy has been shown against symptoms of infection with at least three different viruses.

For at least the reasons provided above, Applicant respectfully requests withdrawal of the rejection of claims 3-9, as amended, under §112, first paragraph.

Claim Rejections – 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless-
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. **(Prior Rejection- Maintained)** The Examiner maintained the rejection of claims 1 and 2 under 35 U.S.C. 102(b) as being anticipated by Avtushenko et al., J Biotechnol. 44: 21-28. Applicant previously traversed the rejection on the grounds that claims 1 and 2 require heat inactivation of the viral pathogen, and that the reference does not teach heat inactivation. The Examiner found this argument in traversal was not persuasive because the claims are drawn to a composition, and not to a method of making the composition. It is not clear, according to the Examiner, how the claimed compositions are structurally distinct from those of the Avtushenko reference.

According to the MPEP, "the *prima facie* case [of obviousness] can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product." MPEP 2112.01, citing *In re Best.*

The term "denatured at higher than 60°C" relates to the end-state composition and is not merely a method of making the composition. That is, the end-state composition resulting from thermal denaturation of the viral pathogen is not the same composition as the end-state composition resulting from forming an emulsion, which is the method of Avtushenko et al. The difference between the two forms of denaturation is vividly illustrated in common experience by two well-known method of hen's egg white denaturation. Egg whites may be beaten to a froth (e.g. a meringue) and thereby denatured on air-liquid interfaces (analogous to an emulsion). The result is cells of air stabilized by a thin coat of surface-denatured protein. Alternatively, egg

whites may be cooked (thermally denatured) to form a compact, rubbery mass. The resulting compositions are different because the egg white protein has denatured to different end-states. The difference in end-state composition is also reflected in another protein, human growth hormone. Katakam et al., J. Pharm. Sci. (1995) 84:713 (Abstract only). Growth hormone is protected against interface denaturation by the presence of surfactants. *Id.* Surfactants, however, do not protect against thermal denaturation. *Id.* Thus, the compositions are different. Similarly, thermally denatured virus pathogen is not the same as emulsion-denatured virus pathogen.

The specification states: "The present inventor considers that the denaturation treatments by heat or with the agents reduces the molecular weight of the antigen and destroys its steric molecular structure...." Page 30, ll. 9-12. Indeed, the structure-altering properties of heat on the proteins and other macromolecules which comprise antigens are well-known to those of skill in the art. Thus, the denaturation inactivation produces a composition that has essential properties that are different from those of antigen that is not heated. Thus heating changes the composition.

An article by Epand and Epand reports the thermal denaturation of influenza virus. Epand et al., Biochem. J. (2002) 365, 841-848. Epand et al. measured thermal transitions in influenza A virus using differential scanning calorimetry, circular dichroism, and SDS gel electrophoresis. *Id.* The authors observed multiple transitions including "the major transition at 60.1°C" at pH 5. *Id.* at 843. The major transition corresponds to denaturation: "[T]he abrupt change observed at pH 7.4 and at approximately 60°C is not seen with the cleaved virus. The conformational changes observed at both pH 7.4....and pH 5...with the intact virus are irreversible upon cooling." *Id.* at 844. The data of Epand et al. show that the inherent properties of influenza virus are such that one of skill in the art would have avoided treatment at higher than 60°C. Moreover, one of skill in the art would have avoided denaturing the virus, because vaccinologists strive to maintain structural features of the antigen so as to elicit an immune response to native virus. This immune response is needed to fight any subsequent exposure to live virus.

Avtushenko et al., by contrast does not teach the heat inactivated viral antigens of the invention. Rather, Avtushenko et al. teaches "emulsion-inactivated" vaccine. (See p. 21, Abstract and p. 22 Materials and Methods).

Furthermore, claim 1 as amended is drawn to a vaccine comprising influenza antigens denatured at higher than 60°C. Avtushenko et al. does not teach influenza antigens denatured at higher than 60°C. Claim 2 has been cancelled.

For at least these reasons, withdrawal of the rejection is requested.

10. **(Prior Rejection- Maintained)** The Examiner has maintained the rejection of claims 3-5, and 7-8 under 35 U.S.C. 102(a) as being anticipated by Barrett et al. (WO 00/47222, see U.S. Patent 6,635,246 for English translation of the specification of the reference). According to the Examiner, these claims read broadly on immunogenic compositions comprising a reduced influenza virus (see above), or an immunogen derived from an influenza virus.

Claims 3 and 5, as amended, are directed to a viral pathogen or an immunogen, respectively, denatured at higher than 60°C and formulated as an oral pill.

By contrast, the influenza virus of Barrett et al. is inactivated as follows: "formalin (final concentration 0.025%) was added and the viruses were inactivated at 32°C, for 24 hours." Col. 4, ll. 25-27. That is, Barrett et al. uses formaldehyde to inactivate the virus.

Barrett's step of warming the virus to less than mammalian body temperature does not qualify as thermal denaturation. A formaldehyde-inactivated virus is not the same as a thermally denatured virus, because the compositions differ in antigen structure.

The gentle warming step used by Barrett et al. to prepare antigen does thus not anticipate the denatured viral pathogen of claim 3, as amended, or the immunogen of claim 5 as amended, which are both thermally denatured at higher than 60°C.

Claims 4 and 7-8, which depend from claims 3 and 5, respectively, incorporate all the limitations thereof.

For at least the reasons provided above, Applicant respectfully requests that Examiner withdraw the rejection over Barrett et al.

11. **(Prior Rejection- Maintained)** Claims 5-8 were rejected by the Examiner under 35 U.S.C. 102(b) as being anticipated by Waldman et al. (Am J Med Sci. 292: 367-71). According to the Examiner these claims read on oral immunogenic compositions comprising an influenza antigen. The Examiner states that Waldman teaches such a composition on page 368.

Waldman et al. discloses administration of enteric-coated capsules of a commercially available commercial trivalent ether-treated influenza vaccine. P. 368. "The capsules were dipped in an enteric coating of cellulose acetate phthalate..." *Id.* The Examiner asserts that pills encompass capsules.

Unlike the Waldman et al. reference, claim 5 as amended is not directed to enteric-coated capsules of influenza vaccine but to immunogen formulated as a pill. A pill differs from a capsule in both structure and the way it works. A capsule is "a structure in which something is enclosed, such as a hard or soft, soluble container of suitable substance, for enclosing a dose of medicine". *www.merckmedicus.com/pp/us/hcp/thcp-dorlands-content.jsp*. Thus, a pill and a capsule are easily distinguishable. The term "pill" as used in this application does not include gelatin capsules. Thus, Waldman et al. can neither anticipate the claimed invention, nor render it obvious.

Moreover, claim 5 is directed in part to an immunogen denatured at higher than 60°C, which immunogen can be influenza virus. The structure and hence the immunogenic composition of ether-inactivated influenza must differ from thermally denatured immunogen.

Thus, Waldman et al. does not disclose all the elements of the claim and cannot anticipate the claim.

Withdrawal of the rejection is requested.

Claim Rejections – 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the difference between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. **(Prior Rejection- Maintained)** Claims 1-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Zakay-Rones et al. (WO 97/14434) or Dutcher et al. (U.S. Patent 3,060,094), either of these references in view of Smith et al. (U.S. Patent 6,245,532) or Avtushenko et al., and further in view of Sokoll et al. (U.S. Patent 6,623,764). According to the Examiner, claims 1-9 read on immunogenic compositions formulated for oral administration or as oral pills.

Sokoll et al. broadly teaches in the Summary of the Invention "an immunogenic composition" which is "a controlled or delayed release vaccine preparation in stable particulate form". Col. 6, ll. 45-46 and 51-53. "The particles are microspherical and contain a matrix of biodegradable polymer and antigen(s) and/or antigen plus co-adjuvant-containing regions." *Id.* at ll. 54-55. Sokoll et al. does not teach a thermally inactivated immunogen. In particular, Sokoll et al. does not teach thermally denatured immunogen.

The references by Sokoll et al, Avtushenko et al, Smith, Zakay-Rones et al, and Dutcher et al. do not singly or in combination supply the elements of independent claims 1, 3 and 5, as amended. In particular, none of Sokoll et al., Avtushenko et al., Zakay-Rones et al., Smith, or Dutcher et al. disclose an immunogen, composition, or a vaccine in which the composition comprises antigen modified by denaturing at higher than 60°C.

Zakay-Rones et al. uses a *combination* of formalin and *mild warming* (45 to 59°C) to inactivate influenza virus. At p. 4, ll. 6-14.

One of skill in the art would recognize that mild warming, e.g. at 45 to 59°C, differs fundamentally from thermal denaturation. Indeed, the purpose of crosslinking antigens with warm formaldehyde is to maintain three-dimensional structure by introducing intra-chain and inter-chain bridges. Thermal denaturation by contrast destroys steric molecular structure and often unravels macromolecules. Thus the claims are not obvious because the combination of the art of record does not teach all the elements of the amended claims. Moreover, the prior art of record cannot lead one of skill in the art to use compositions having thermally denatured immunogen. The dependent claims incorporate all the limitations of the independent claims from which they depend, and thus are not obvious.

For at least the above reasons, withdrawal of the rejection is requested.

14. **(Prior Rejection- Maintained)** Claims 5-9 were rejected by the Examiner under 35 U.S.C. 103(a) as being unpatentable over Sokoll (supra).

Withdrawal of the rejection is requested for at least the reasons provided above.

15. **(Prior Rejection- Maintained in part)** Claim 9 was rejected under 35 U.S.C. 103(a) as being unpatentable over the teachings of either Barrett et al. as applied above against claims 3-5, 7, and 8, Avtushenko et al. as applied against claims 3-4, or Waldman et al. as applied against claims 5-8. Applicants appreciate the withdrawal of the rejection of claim 9 over Avtushenko et al.

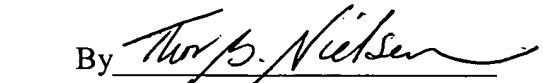
Withdrawal of the rejection over the remaining references is respectfully requested for at least the reasons presented above.

In view of the above amendments, Applicant respectfully requests allowance of claims 1 and 3 to 9.

Applicant hereby authorizes the Commissioner to please charge our Deposit Account No. 22-0185, under Order No. 22220-00003-US in the amount of $455 for a one month extension of time and Request for Continued Examination and any other fees deemed necessary, from which the undersigned is authorized to draw.

Dated: June 8, 2005

Respectfully submitted,

By 

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